SUMMARY

I. TITLE

A Randomized, Double-Blind, Parallel Group, Analgesic Efficacy, Safety, Acceptability and Quality of Life Study of Fixed Doses of Controlled-Release Oxycodone Tablets Versus Placebo in Chronic Non-malignant Pain Due to Osteoarthritis

II. INVESTIGATORS

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III. TRIAL DATES

Clinical enrollment in study OC92-1102 began on June 15, 1993. The last patient completed on April 15, 1994.

IV. OBJECTIVES/STUDY DESIGN

The objective of this study was to assess the analgesic efficacy, safety, acceptability, quality of life and oxycodone pharmacokinetic/pharmacodynamic profiles in patients with moderate to severe pain related to osteoarthritis.

This was a double-blind, randomized, placebo-controlled, repeated-dose, parallel group study. The three groups of patients were dosed q12h with placebo or 10 mg tablets of Controlled-Release Oxycodone at 10 and 20 mg q12h levels. Patients who were randomized were scheduled to receive 14 days of dosing. No titration or rescue were allowed.

V. STUDY POPULATION/DISPOSITION

One hundred and thirty-three (133) patients, 18 years of age or older, who had a diagnosis of osteoarthritis confirmed by clinical and radiographic criteria, with an average current pain intensity of moderate or greater, were enrolled at seven study centers, all in the United States.

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The average age was 62 years old. A total of 116 of the 133 (87%) enrolled patients were white and 98 (74%) were female. The predominant osteoarthritic sites were spine/back (46%) and knee (31%).

Disposition of Patients: One hundred and thirty-three (133) patients were admitted and randomized into the study; 63 patients completed the trial (three of the 63 were protocol violators); 70 patients discontinued prematurely: 39 because of ineffective treatment, 28 because of an adverse experiance, 2 were protocol violators, and 1 for other reasons.

VI. RESULTS

Study Regimen:

Patients were randomly assigned to either two matching placebo tablets, a CR Oxycodone tablet 10 mg plus a placebo tablet, or two CR Oxycodone Tablet 10 mg q12h for 14 days, based on a randomization list provided by the Biostatistics and Clinical Data Management group at The Purdue Frederick Company.

Efficacy Results:

The first and most general measurement of analgesic effectiveness is patients who prematurely discontinue because of lack of efficacy. In this regard, 49% of patients in the placebo group as compared to 27% in the CR Oxycodone 10 mg q12h group and 11% in the CR Oxycodone 20 mg q12h group discontinued because of lack of efficacy.

The overall mean Pain Intensity over the study period was the primary efficacy variable. Table I summarizes the arithmetic mean pain intensities for each analysis population. Figure I presents the mean daily pain intensity by study day for the extrapolated population.

Table I: Mean Pain Intensity Scores

	Placebo	CR Oxycodone 10 mg	CR Oxycodone 20 mg
Completed			
Baseline	2.33	2.59	2.45
Week 1	1.64	1.96	1.44
Week 2	1.61	1.70	1.40
Overall	1.62	1.83	1.42
Extrapolated			

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Table I: Mean Pain Intensity Scores

	Placebo	CR Oxycodone 10 mg	CR Oxycodone 20 mg
Baseline	2.38	2.53	2.49
Week 1	2.05	2.02	1.60
Week 2	2.09	1.91	1.61
Overall	2.07	1.96	1.60
Intent-to-Treat			
Baseline	2.35	2.45	2.41
Week 1	2.04	1.99	1.64
Week 2	1.71	1.67	1.40
Overall	2.03	1.93	1.63

0 = No pain, 1 = Slight, 2 = Moderate, 3 = Severe

The analysis of covariance (ANCOVA) showed statistically significant treatment effect on Week 1 ($p=0.015$) and Overall ($p=0.015$) for the Intent-to-Treat population, where the CR Oxycodone 20 mg was better than placebo and CR Oxycodone 10 mg as indicated by the pairewise and treatment versus control comparison procedures. Similar results were seen for the Efficacy and Safety (extrapolated) population (including discontinued patients who had last observation carried forward). No significant statistical differences among the treatment groups were revealed for the Efficacy and Safety (completed) patients.

The graphic representation of the daily mean pain intensity scores demonstrates a relatively rapid reduction in pain intensity in the CR Oxycodone 20 mg q12h group. This value falls from 2.49 to 1.88 over the first 24 hours and by day 3 represents 94% of the peak reduction in mean pain intensity realized over the 14 day trial. The mean pain intensity in the CR Oxycodone 10 mg q12h group falls at a slower and somewhat more steady fashion, falling from 2.53 to 1.97 over the first 5 days. The placebo response in extrapolated population, parallels the low dose (10 mg q12h) group. After day 5 the placebo group shows no further reduction in mean pain intensity and in fact was increased on all of the remaining 9 days. Over the same final 9 days, the CR Oxycodone 10 mg q12h group was consistently (but not statistically) better than placebo.

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PDD8001015219

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The intent-to-treat population showed that CR Oxycodone 20 mg q.12h. had a significantly greater Acceptability of Therapy ($p < 0.05$) than placebo in Week 1 and Overall. A statistically significant treatment effect was found in Week 1 for the Efficacy and Safety (completed) population, where both placebo and CR Oxycodone 20 mg were better ($p < 0.05$) than CR Oxycodone 10 mg. For the extrapolated population, CR Oxycodone 20 mg was better ($p < 0.05$) than placebo in Week 1, Week 2, and Overall.

For the Intent-to-Treat population, the CR Oxycodone 20 mg group had significantly better ($p < 0.05$) Quality of Sleep than placebo group over the study period. Overall, no statistically significant differences between CR Oxycodone 10 mg and the other two groups were revealed, while on Week 2 the 10 mg group had significantly lower quality of sleep than the other two groups and had more Awakenings than the Placebo group.

For the Health Assesement Questionnaire, which defines Quality of Life parameters (Brief Pain Inventory and Activities and Lifestyle), statistically significant ($p < 0.05$) treatment effects were found. For Week 1, CR Oxycodone 20 mg was significantly better than placebo with respect to pain at its worse, pain right now, and pain on the average and interference with sleep. CR Oxycodone 20 mg was also significantly better than CR Oxycodone 10 mg for pain right now. For Week 2, CR oxycodone 20 mg was significantly better than placebo for each of the same items at Week 1. In addition, CR Oxycodone was significantly better than placebo for pain at its least and interference with mood. CR Oxycodone 20 mg was also significantly better than CR Oxycodone 10 mg for pain at its worse and pain at its least. Also, CR Oxycodone 20 mg was significantly better than placebo at Week 1 in reducing "burning" and "tender" pain as well as patients rating themselves "miserable".

While, relative to placebo improvements, neither active treatment group was able to further significantly improve the functional assessments measured in the Activities and Lifestyle Questionnaire, it should be noted that CR Oxycodone did not impair the patient's ability to conduct these tasks as compared to placebo. These tasks included getting dressed (including shoelaces and buttons), getting in and out of bed, lifting a glass, walking outdoors on flat ground, washing and drying the entire body, bending down to pick up clothing, turning faucets on and off, and getting in and out of the car. It should also be noted that since most of these activities were conducted "without any difficulty" or "with some difficulty" there was little room for improvement in these functional activities.

Pharmacokinetics/Pharmacodynamics

Mean plasma oxycodone concentrations at 0 and approximately 3 hours with q12h placebo, 10 and 20 mg CR Oxycodone were 0 and 0 ng/ml, 8 and 16

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PDD8001015220
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ng/ml, and 16 and 30 ng/ml, respectively. There was an approximate two-fold fluctuation between the mean concentrations at trough and approximate peak concentrations for both the 10 and 20 mg q12h dosages. In addition, there was a two-fold difference in trough concentrations with a doubling of dose, providing a demonstration of dose-concentration proportionality.

Mean pain intensity (VAS) scores (mm) at approximately 0 and 3 hours with q12h placebo, 10 and 20 mg CR Oxycodone were 53.60 and 45.56, 47.09 and 41.97, and 36.97 and 25.37, respectively. The histogram presentation of plasma oxycodone concentration and pain intensity (VAS) can be seen in Figure II. The corresponding categorical scores indicate that, on the average, pain was reported as 1.94 and 1.72 with placebo, 1.70 and 1.60 with 10 mg and 1.52 and 1.15 with 20 mg q12h. This is in contrast to pretreatment pain intensity scores approximating 2.35, 2.45, and 2.41. CR Oxycodone was therapeutic in a dose-proportional manner in the improved control of moderate to severe pain.

The regression of categorical and VAS pain intensity scores on log plasma oxycodone concentrations resulted in statistically significant correlations. As the mean plasma oxycodone concentrations increased, the pain intensity scores decreased in a consistent manner. While regression of the MSDEQ (which primarily assesses subjective drug effects) parameters on oxycodone concentrations provided for statistically significant correlations in many cases, these were of low predictive value. This may be related to the limited effect of oxycodone on most of these effects at the doses utilized. In general, the subjective drug effects reported by the patient and observed by the investigator were of such low magnitude that they were judged to be of little clinical significance.

Two (2) metabolites of interest (oxymorphone and noroxycodone) were examined. Mean noroxycodone concentrations were 78-108% of the parent oxycodone concentrations while oxymorphone concentrations were 2.1-3.9% of the parent oxycodone concentrations. In general, these metabolites increased in parallel with increasing plasma oxycodone concentrations.

Safety Results:

One hundred and thirty-three (133) patients were included in the safety analysis. Safety was evaluated by examination of deaths, adverse drug experiences (ADEs), drop-outs because of ADEs, laboratory analyses, vital signs and physical examinations.

There were no deaths during this 14 day trial.

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Discontinuations due to adverse experiences were reported in 4% of placebo, 27% of CR Oxycodone 10 mg q12h and 32% of CR Oxycodone 20 mg q12h patients. These events, resulting in premature discontinuation, were predominantly gastrointestinal (nausea, vomiting) and central nervous system (drowsiness).

Treatment-related ADEs were reported in 65% of patients (40% of placebo patients, 75% of CR Oxycodone 10 mg q12h patients and 82% of CR Oxycodone 20 mg q12h patients). The body systems most commonly involved were the digestive and nervous system. The most common ADEs can be seen in Table 2. These events were typical opioid adverse effects. The common gastrointestinal events appeared to be dose-related, while no apparent dose-relationship was evident with the common CNS events. Using a logistic regression model there were no statistically significant differences in these ADEs in males vs. females. In patients ≥65 years old vs. <65 years old, only somnolence was significantly more prevalent in elderly patients (but not dose-related).

TABLE 2

Adverse Drug Experience	Placebo N = 45	CR Oxycodone 10 mg q12h N = 44	CR Oxycodone 20 mg q12h N = 44
Nausea	5 (11%)	12 (27%)	18 (41%)
Constipation	3 (7%)	10 (23%)	14 (32%)
Somnolence	2 (4%)	11 (25%)	12 (27%)
Vomiting	3 (7%)	5 (11%)	10 (23%)
Dizziness	4 (9%)	13 (30%)	9 (21%)
Pruritus	1 (2%)	8 (18%)	7 (16%)
Headache	3 (7%)	4 (9%)	5 (11%)
Dyspepsia	0 (0%)	3 (7%)	3 (7%)
Nervousness	0 (0%)	3 (7%)	0 (0%)

Analyses of laboratory findings, vital signs and physical examinations revealed no clinically meaningful safety concerns.

VII. CONCLUSIONS:

This study enrolled 133 patients with osteoarthritis-related pain. The results clearly showed that CR Oxycodone 20 mg is an effective analgesic when administered every 12 hours as compared to placebo.

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In this study, CR Oxycodone at a dose of 20 mg q12h was superior to CR Oxycodone 10 mg q12h and placebo in reducing pain intensity. CR Oxycodone 10 mg q12h was not able to demonstrate statistically significant differentiation from placebo in this model. However, the mean daily pain intensity in this group showed a consistent reduction in pain intensity that was greater than that seen with placebo. In fact, by day 14, the CR Oxycodone 10 mg, q12h group had pain intensity reduced by 0.67 categorical units from baseline, a reduction which is sufficient to demonstrate analgesic activity in many trials. However, the placebo response of 0.29 categorical units over this 2 week trial was less and blunted the ability to declare statistical significance.

The Brief Pain Inventory, which has been widely used and validated as a pain and quality of life tool consistently supported the analgesic activity of the CR Oxycodone 20 mg, q12h group. This Inventory also showed a significant effect of the CR Oxycodone 20 mg, q12h group in improving quality of life by reducing the interference by pain on mood and sleep. The Activities and Lifestyle assessment indicated that opioid therapy did not interfere with these patients' day-to-day functional activities.

CR Oxycodone 20 mg q12h had significantly improved acceptability of therapy and quality of sleep compared to placebo.

Pharmacokinetic evaluations demonstrated dose-proportionality in this out-patient, chronic, non-malignant pain population. Upon repeated dosing, the trough concentration of oxycodone was approximately 50% of the apparent peak concentration. There was a statistically significant correlation between plasma oxycodone concentrations and pain intensity (both VAS and categorical scale). Finally, the metabolites (oxymorphone and noroxycodone) parallel plasma oxycodone concentration at 2.1-3.9% and 78-108% of the parent concentration, respectively.

While regression of the MSDEQ (which primarily assesses subjective drug effects) parameters on oxycodone concentrations provided for statistically significant correlations in many cases, these were of low predictive value. This is related to the limited effect of oxycodone on most of these effects at the doses utilized.

In this population, 4% of the placebo patients, 27% of the CR Oxycodone 10 mg q12h group and 32% of the CR Oxycodone 20 mg q12h patients discontinued because of ADEs. The greater number of reports with CR Oxycodone were primarily due to the opioid-related side effects of nausea, vomiting, dizziness and somnolence.

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There were no significant safety observations concerning laboratory findings, changes in vital signs or physical examinations.

This study has demonstrated that CR Oxycodone is a safe and effective analgesic for the control of osteoarthritis-related pain.

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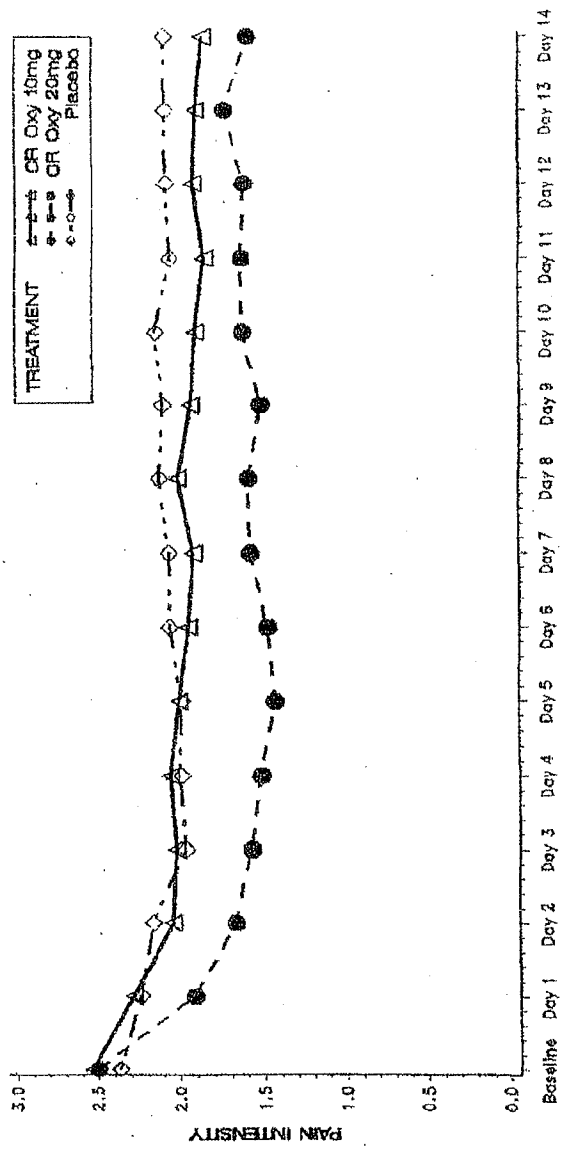
FIGURE I

MEAN DAILY PAIN INTENSITY

Population: Extrapolated Patients Valid for Safety and Efficacy



CROSS REFERENCE
Study Report: Figure 1.2 and Table 5.2

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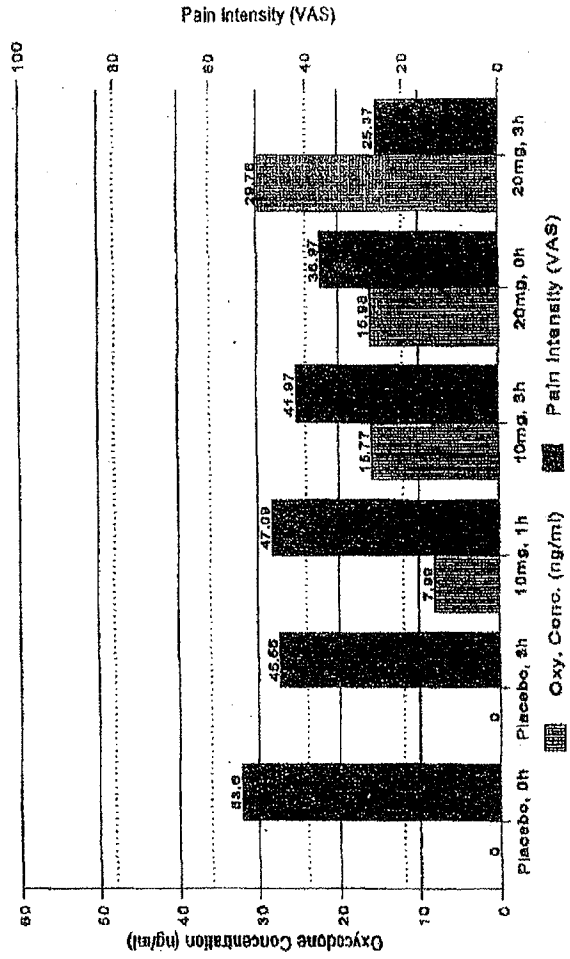
PROTOCOL NO. OC92-1102:
FIGURE II
TIME-PAIRED MEAN OXYCODONE CONCENTRATION AND PAIN INTENSITY (VAS) RANKED BY INCREASING CONCENTRATION
Population: Patients Valid for PK/PD



Cross Reference: Figure 4.1 & Table 14.1

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